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10/798,090

03/11/2004

Ivan Richards

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6030

65778

7590

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EXAMINER

BOWMAN, AMY HUDSON

ART UNIT

PAPER NUMBER

1635

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/798,090	<b>Applicant(s)</b> RICHARDS ET AL.	
	<b>Examiner</b> AMY BOWMAN	<b>Art Unit</b> 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 19 April 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1, 14, 16, 17, 19-21, 30-45, 48 and 49 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 14, 16, 17, 19-21, 30-45, 48 and 49 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 March 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of Application/Amendment/Claims***

Applicant's response filed 4/19/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/18/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant has added claims 48 and 49. Therefore, claims 1, 14, 16, 17, 19-21, 30-45, 48 and 49 are pending in the application.

Applicant's amendments and/or arguments filed on 4/19/08, with respect to the rejections under 35 USC 112 have been fully considered and are persuasive. Therefore, these rejections have been withdrawn. However, the following rejection is maintained and upon consideration of the instant amendments, a new grounds of rejection is applied as set forth below.

### ***Priority due to claim amendments***

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. None of the priority documents teach a limitation wherein any of the purine nucleotides are “differentially” modified at a 2'-sugar position from any of the pyrimidine nucleotides at a 2'-sugar position.

Application 60/363,124 does not teach the instant limitations of “one to ten or more”, as recited in instant claim 42, or “are differentially modified”, as recited in claim 1; or “50 percent or more”, as recited in claim 1; or “at least 35%”, as recited in claim 44.

The examiner has explained that application '124 does not offer support for the claimed range. Specifically, application '124 does not teach the limitation "50 percent or more" of the nucleotides of each strand have the claimed modifications or "35%" of the nucleotides of each strand have the claimed modifications or “one to ten or more” of the pyrimidine nucleotides in each strand are specific modifications. Although application '124 sets forth examples that fall within the instant scope, the application does not support the instant breadth.

It is agreed that examples are readily derivable within application '124 that fall within the instant ranges. However, this is not support to cover the instantly recited ranges, which also include many percentages that are not taught or exemplified by application '124. Furthermore, the specific examples do not support the vast possibility of combinations of chemical modifications at the varying percentages as instantly recited.

Applicant has amended the claims to recite "any" of the purine nucleotides are differentially modified with a 2'-sugar modification that differs from that of any of the pyrimidine nucleotides. However, the term "any" is not supported by application '124 because "any" can include any quantity of modification, which is not taught by the '124 application.

Furthermore, application '124 does not teach or define "differentially" modifying nucleic acid molecules and this terminology embraces a huge possible genus of modifications.

Furthermore, the documents do not teach that "at least two of the modifications are different from each other", as recited in claim 44.

Therefore, instant claims 1, 14, 16, 17, 19-21, 30-41, 44, 45, 48 and 49 are accorded an effective filing date of 3/11/04, which is the filing date of the instant application. Instant claims 42 and 43 are accorded an effective filing date of 2/20/03, which is the effective filing date of PCT/US03/05028, the earliest filed document that supports each limitation of claims 42 and 43.

Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation in each of the claimed priority documents.

***Response to Arguments--Claim Rejections - 35 USC § 103***

Claims 1, 14, 16, 17, 19-21, 30-45, 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), in view Nyce (WO 99/13886), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Matulic-Adamic et al. (US 5,998,203), Kurreck et al. (Nucleic Acids Research, 2002, Vol. 30, No. 9, pages 1911-1918), Bertrand et al. (Biochemical and Biophysical Research Communications, 2002, 296, pages 1000-1004), Braasch et al. (Biochemistry, 2002, Vol. 41, No. 14, pages 4503-4510), and Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109).

It is noted that the Elbashir et al., Nyce, and Parrish et al. references are of record and cited on the PTO-892 mailed on 7/24/06; and the Kurreck et al., Bertrand et al., Braasch et al., and Olie et al. references are of record and cited on the PTO-892 mailed on 12/28/07.

It is noted that newly added claims 48 and 49 are rejected because they recite the same types of modifications that have been already addressed in the pending rejection. Newly added claim 48 requires for "any", which requires at least one of the purine nucleotides to be a 2'-O-methyl and at least one of the pyrimidines to be a 2'-

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deoxy-2'-fluoro. Newly added claim 49 requires for the nucleotides to be modified with 2'-deoxy-2'-fluoro, 2'-O-methyl, or 2'-deoxy modifications.

Applicant argues that the Olie, Braasch, Bertrand and Kurreck references are not proper prior art as these references were published after the priority date of the '124 application. Contrary to applicant's argument, the instant claims do not receive benefit of the '124 application, as explained in the "Priority due to claim amendments" section above.

Applicant asserts that Elbashir et al. teaches away from the instant invention. Applicant points to page 6885, left column of Elbashir et al. and cites the following passage: "[m]ore extensive 2'-deoxy [aside from substitutions of the 2 nt 3'-overhanging ribonucleotides] or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly." Applicant continues to argue the interpretation of this passage. It is noted that the underlined portion of the passage was inserted by applicant and is not actually present in the passage of Elbashir et al. The examiner is not willing to read other percentages or results into the passage that were not reported on or taught by Elbashir et al. The passage cited by applicant is interpreted by the examiner completely within the context context of the article, which teaches successful inhibition with certain modifications and unsuccessful inhibition with 100% modification of 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. is silent to any other percentages between those that resulted in successful inhibition and 100% modification with 2'-deoxy or 2'-O-methyl modifications that abolished activity.

Elbashir et al. teaches that “2'-deoxy substitutions of the 2 nt 3'-overhang ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.” This passage is interpreted by the examiner in a consistent manner with the rest of the article, which teaches either modifying the terminal nucleotides or modifying 100% of either strand. Therefore, Elbashir et al. teaches the benefits of modifying the 2 nt 3'-overhangs and then teaches that the more extensive modification that was tested, which is 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications reduced the ability of siRNAs to mediate RNAi. The examiner is not speculating on the interpretation of Elbashir et al. but is rather interpreting it as it is written. Applicant is adding statements into the citation to draw their own conclusions. Elbashir et al. does not teach any chemical modification percentages other than 19 percent or 100% of one or both strands.

Furthermore, the successful teachings of Elbashir et al. combined with the teaching of Elbashir et al. that substitutions helped to reduce cost and may enhance RNase resistance would certainly offer motivation to one of skill in the art to try modifications at varying percentages between the 19% successful modification and 100% unsuccessful modification with 2'-deoxy or 2'-O-methyl modifications and thus Elbashir et al. does not teach away as asserted by applicant.

Applicant asserts that although Parrish et al. teach a 26 bp siRNA, Parrish did not teach modification of the 26 bp siRNA. It is noted that this is consistent with the



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interpretation set forth by the examiner, wherein the examiner did not assert that Parrish et al. teach modification of the 26 bp siRNA. Applicant asserts that Parrish described 2'-deoxy-2'-fluoro uridine modifications, but not 2'-deoxy-2'-fluoro cytidine modifications and further taught that 2'-deoxy modification of cytidine was detrimental to RNAi activity. In response, it is noted that the features upon which applicant relies (i.e., uridine vs. cytidine modification) are not recited in the rejected claim(s). Therefore, applicant is arguing a limitation that is not instantly recited. Furthermore, although Parrish et al. teaches that 2'-deoxy modification of cytidine produced a decrease in RNAi activity, the activity was not abolished. In Figure 5 of Parrish et al., strands modified with 2'-deoxy modification of cytidine resulted in "++" unc-22 interference, wherein "+++" is the maximum interference. Since modifications are known in the art to benefit nucleic acid inhibitory molecules, one of skill would have certainly been motivated to incorporate these modifications at varying percentages and combinations, as well as in various locations of the duplex, given that they did result in interference activity when incorporated into dsRNA molecules that act via RNAi, as evidenced by the teachings of Parrish et al.

Applicant asserts that Parrish et al. does not teach modification of both strands, but rather modification of the sense or antisense strand and does not teach 2'-O-methyl modification, and does not teach differentially modifying. It is noted that this is a rejection under 35 USC 103(a) rather than under 35 USC 102. Parrish need not teach each and every limitation of the instant claims to be pertinent in a rejection under 35 USC 103(a). It is noted that the examiner did not rely upon Parrish et al. for teaching

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modification of both strands but rather for offering motivation to try, in combination with the other references cited by the examiner, to extensively modify the duplex (one or both strands) with chemical modifications that are known to benefit the stability and delivery of nucleic acid inhibitory molecules and are known to be tested to routinely optimize such molecules. The instant specification does not define the term “differentially” modified. This terminology is interpreted as incorporating a modification that is different from another nucleotide. Therefore, a 2'-modification of a purine nucleotide must be different from a 2'-sugar of a pyrimidine nucleotide. It is considered obvious and certainly within the realm of routine optimization to combine known chemical modifications within the instantly huge genus of modifications at various percentages into different configurations. Applicant has not provided any unexpected result commensurate in scope with the instant genus to demonstrate that the instant genus is not simply a combination of known chemical modifications in various configurations. Importantly, the instant claims are not directed to any specific combination of modifications in any specific configuration.

Applicant argues that Bertrand et al. did not achieve comparable results between antisense oligonucleotides and siRNAs based upon teachings of a vectorized antisense that inhibited GFP, wherein the siRNA did not. Applicant concludes that therefore one could not sue the same practices applied to antisense and get predictable results with siRNAs. The examiner did not assert that antisense oligonucleotides and siRNAs will always yield the same result, but rather that it is known in the field that they both face similar delivery challenges, as they are both inhibitory nucleic acid molecules, which is

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evidenced by the teachings of Bertrand et al. Parrish et al. and Elbashir et al. are evidence that it is known in the siRNA field to test modifications that enhanced the activity of antisense oligonucleotides on dsRNA molecules.

Bertrand et al. teach a comparison of antisense oligonucleotides and siRNAs. Bertrand et al. teach that siRNAs appear to be quantitatively more efficient with a longer lasting effect *in vitro* than antisense oligonucleotides. Bertrand et al. teach that siRNA activity, but no antisense oligonucleotide activity, was observed in mice, probably due to the lower resistance to nuclease degradation of antisense oligonucleotides (see abstract). Bertrand et al. teach that siRNAs are composed of small double-stranded RNA oligonucleotides with a length of 21/22 bases (see page 1000, column 1). Bertrand et al. teach that delivery is a very similar issue for both approaches and that siRNAs are very promising tools for gene inhibition *in vivo* (see page 1000, column 2). The examiner is not relying upon Bertrand et al., or any other single reference, for teaching that antisense oligonucleotides are identical in chemistry with siRNAs, but rather that it was known in the art that they both face similar delivery challenges, and that it was known to try modifications that had enhanced the activity of antisense oligonucleotides in siRNA molecules.

Importantly, the examiner has not asserted that any known modification from antisense or ribozyme art will give predictable results without routine testing to determine locations and amounts that will result in RNAi activity. The examiner has rather asserted that incorporating known modifications from the antisense or ribozyme art is considered obvious within the instant huge genus of possibilities and that it is

considered within the realm of routine optimization to determine amounts/locations optimal for activity, as evidenced by the experiments of Parrish et al.

This is supported by the instant specification as well, as the instant specification discloses a multitude of oligonucleotide and ribozyme art regarding chemical modifications and teaches that "Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of these teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited." (see page 100).

Applicant asserts that Olie et al. is specific to enhancing the activity of oligonucleotides that activate RNase H. Importantly, the examiner did not assert anything to the contrary. Olie et al. teach that gapmer chemistry is an optimal format and that these findings may have implications for the design and development of antisense oligonucleotides. Olie et al. teach that 2'-O-modifications provide additional nuclease resistance to oligonucleotides. Olie et al. teach synthesis of 20-mer chimeric antisense oligonucleotides. The teachings of Olie et al. support that routine optimization of nucleic acids is needed to determine the optimal type or location for activity. The fact that antisense oligonucleotides or ribozymes act via a different mechanism than RNAi molecules is irrelevant in view of the fact that they are each nucleic acid inhibitory molecules that each face delivery challenges. Importantly, each of these types of

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molecules have been modified with the same types of modifications before the instant invention, as evidenced by the teachings of the references relied upon by the examiner.

The question is not whether one would incorporate modifications known to enhance the activity of antisense oligonucleotides or ribozymes into dsRNAs that act via RNAi, as this has already been taught by Parrish et al. and Elbashir et al. The question is rather if combining such modifications in different configurations and at different percentages is considered obvious. Since it is known that different types of modifications yield different results at different locations within a nucleic acid compound, whether the compound be an antisense oligonucleotide, a ribozyme, or a RNAi compound, it is considered within the realm of routine optimization to incorporate varying percentages and combinations of modifications known to enhance nucleic acid inhibitory molecules in order to determine the optimal combination/configuration.

Although applicant argues the individual teachings of each reference, it is the combination of the references that renders the instant genus obvious since applicant is not claiming any specific configuration of any specific modifications. Furthermore, contrary to applicant's assertions regarding "differentially" modifying nucleotides, Parrish et al. teaches specifically modifying cytidines or uracils, for example, as discussed by applicant.

The combined references offer motivation to incorporate the instantly recited chemical modifications into a siRNA duplex at varying percentages/combinations/locations to optimize the activity of the resultant molecule. It was known in the art to incorporate modifications into siRNA molecules that had been

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previously utilized with antisense oligonucleotides and ribozymes and it is acknowledged that routine testing is needed to optimize the activity, as not every combination or placement of modifications is optimal. Although applicant asserts that one could not incorporate a modifications that was known to confer stability to a ribozyme or antisense and apply it to an siRNA with a reasonable expectation that one would obtain an active siRNA, it was known in the art to incorporate modifications from the antisense and ribozyme art into molecules that act via RNAi and result in interference activity, as evidenced by the successful interference reported by Elbashir et al. and Parrish et al. with chemically modified dsRNA molecules. Applicant supports their assertion by pointing to Elbashir et al. and concluding that Elbashir et al. teaches that modifications that were successfully applied to other nucleic acids must be entirely avoided or applied only to the terminal nucleotides. As discussed above, applicant is asserting that Elbashir teaches such a conclusion although Elbashir et al. does not teach that the modifications should be entirely avoided. Furthermore, the fact that Elbashir et al. focused on the terminal regions supports the fact that optimization is needed to determine the proper configurations of such known modifications to result in preferred inhibitory compounds.

Applicant sets forth applicant's interpretation of each of the cited references and what each of the references do not teach. As explained above, this is a rejection under 35 USC 103(a) rather than under 35 USC 102. As such, it is the combination of the cited references that renders the instant claims obvious. Although applicant argues that the references do not teach every limitation, every limitation has been addressed in the

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rejection. Contrary to applicant's assertions, there is a suggestion in the art cited by the examiner that it is beneficial to chemically modify nucleic acid inhibitory molecules including siRNA molecules, the modifications are known in the art, and it is within the realm of routine optimization to determine optimal locations/configurations for the modifications. Although applicant asserts that there was no apparent reason at the time of filing to combine the known elements, this is contrary to the state of the art. As evidenced by Elbashir et al. and Parrish et al., it was known to incorporate modifications that had previously benefited antisense or ribozymes into dsRNA molecules that act via RNAi. The fact that these references teach modifying dsRNA molecules that act via RNAi runs completely contrary to applicant's assertion that there was no reason to modify such molecules.

The routine optimization that is discussed in great detail above is considered to certainly result in molecules with some level of silencing activity in view of the teachings of Elbashir et al. and Parrish et al., wherein silencing was achieved other than when 100% modification was utilized with 2'-deoxy or 2'-O-methyl modifications. Within the instant genus of possible amounts/combinations/types/locations of chemical modifications, one would certainly expect to achieve some molecules that result in silencing activity.

Contrary to applicant's assertions, each of the chemical modifications was known to be utilized to enhance stability and/or delivery of nucleic acid inhibitory molecules. Combining the modifications, incorporating them at varying percentages, or incorporating them on purines or pyrimidines is considered a matter of design choice.

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One of skill would certainly have a reasonable expectation of success for the invention to work for its intended purpose within the instantly recited broad scope of possible combinations and percentages of modifications.

Applicant asserts that because incorporation of chemical modifications was known to not yield predictable results at the time the invention was made in terms of RNAi activity. However, it was known that incorporation of chemical modifications did yield RNAi activity, as evidenced by Elbashir et al. and Parrish et al., wherein in the case of Parrish et al. the dsRNA molecules were extensively modified at cytidine or uracil bases and retained RNAi activity. This supports that there would be a reasonable expectation of success at differentially incorporating modifications on specific bases and at extensive percentages, particularly in view of the instant claim breadth which is not directed to any specific combination of modifications or configuration thereof.

Applicant further argues the application of antisense or ribozyme modifications to siRNA molecules, which is already addressed above. The examiner is not relying upon the usage of the modifications in antisense or ribozyme technology to yield any specific pattern of modification of a siRNA, but rather to demonstrate that it was known to incorporate chemical modifications that were known to add benefits to antisense oligonucleotides or ribozymes into siRNA molecules; it was known within the field of nucleic acid inhibitory molecules in general that routine testing is needed to determine which modifications/configurations are optimal, i.e. not every modification or combination of modifications is going to yield 100% activity and therefore the molecules



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must be optimized. Applicant is not claiming any specific configuration that has shown any unexpected property.

Simply because the teachings of Elbashir et al. regarding the presence of modified overhangs offered motivation in the art to incorporate overhangs and to modify them does not mean that Elbashir et al. teaches away from optimizing the remainder of the molecule via incorporating other known chemical modifications at varying percentages that Elbashir et al. is completely silent to. Applicant is drawing conclusions from the Elbashir et al. reference that Elbashir et al. is silent to.

Although applicant argues that the references do not teach every limitation of the instant claims, it is the combination of the cited references that render the instant claims obvious, as explained in great detail above.

### ***New Rejections***

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 14, 16, 17, 19-21, 30-41, 44, 45, 48 and 49 are rejected under 35

U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

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inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claim 1 is directed to a nucleic acid molecules wherein "any of the purine nucleotides are differentially modified at a 2'-sugar position from any of the pyrimidine nucleotides at a 2'-sugar position." However, the instant specification does not teach this limitation and does not define what is meant by "differentially" modifying the nucleic acid.

Furthermore, claim 44 is directed to nucleic acid molecules wherein "at least two of the modifications are different from each other", which is not taught by the instant specification. Although the specification teaches combinations of modifications, the specification does not teach "at least two" as criteria for the modifications.

Therefore, the effective filing date of claims is considered, for purposes of prior art, to be 3/11/04, which is the filing date of the instant application.

A review of the specification does not reveal support for where the various claim amendments are found and therefore they constitute new matter. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation discussed above.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMY BOWMAN  
Examiner  
Art Unit 1635

AHB

/J. E. Angell/  
Primary Examiner, Art Unit 1635